Author's response to reviews

Title: Influence of retinopathy on the achromatic and chromatic vision of patients with type 2 diabetes

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Author's response to reviews: see over
Influence of retinopathy on the achromatic and chromatic vision of patients with type 2 diabetes

BMC Ophthalmology (Section: Neuro-ophthalmology)

Editor's Comments

1) Please use standard English, not American.
   A) This has been done.

2) Significant correction required.
   A) Corrections have been made as outlined below.

Editor's Additional request

3) Requesting for Copy-Edit. We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.
   A) We hope that the manuscript is now acceptable in the use of standard English language editing. It has been edited by Edanz.
Title: Influence of retinopathy on the achromatic and chromatic vision of patients with type 2 diabetes

Abstract

1) (See some suggested changes to abstract)

Background: Achromatic contrast sensitivity (CS) and color vision (CV) are considered to have great predictive value in the evaluation of type 2 diabetic retinopathy. However, these two visual parameters have seldom been investigated in the same group of patients. In the present study we measured CS and CV in a group of patients with type 2 diabetes and correlated the results with estimates of common metabolic markers for the disease. A subgroup of patients had no clinical signs of retinopathy.

Methods: The vision of twenty-seven patients (n = 50 eyes) suffering from type 2 diabetes, with retinopathy (n = 20 eyes) or without retinopathy (n = 30 eyes), were evaluated using two psychophysical tests: Farnsworth-Munsell 100 hue test (FM 100), and measurement of the luminance contrast sensitivity at 11 spatial frequencies. The results were compared with measurements obtained with an age-matched control group (n = 32) and correlated with the level of glycated hemoglobin, glycemic level, and time of disease. Any signs of retinopathy were identified during the ophthalmological examination.

Results: Contrast sensitivity and color vision impairments were present in different degrees in diabetes patients. Eyes with retinopathy yielded more severe loss than eyes without retinopathy. FM 100 test was more sensitive to separate patients and controls. Color vision loss had no color axes preference. The contrast sensitivity test appears to have some advantage in differentiating patients with retinopathy from patients without retinopathy.

Conclusions: Both methods can be useful to follow the visual function of diabetic patients, and should be used together to discriminate patients and controls as well as to identify early signs of retinal damage.

A) The abstract has been edited and the reviewer’s suggestions have been incorporated into the revised version.

Comments on manuscript

2) The study reports results for contrast sensitivity (CS) and colour vision (CV) tests in a group of patients with type 2 diabetic retinopathy. The selected patients fall into two subgroups: a. those with clear clinical signs of retinopathy, and b. those without. In addition to comparing the relative merits of CS and CV, the authors also examine the correlation with principal metabolic markers in patients with type 2 diabetes. The authors report interesting and useful findings, but the script has grammatical errors and spelling mistakes and would benefit from thorough editing.
A) This was done. An English native speaker corrected the manuscript and it has been edited by Edanz.

3) Some of the comments are too generalised, e.g., These two procedures should be better studied to determine their specificity and sensitivity to diabetic retinopathy. One must distinguish between chromatic and achromatic mechanism and the ability to use achromatic and colour tests of CS and CV that will differ widely in sensitivity and this in turn may affect specificity in relation to detection of abnormal changes that can be linked to the earliest vision losses in diabetes.

A) We inserted in the Introduction section the following sentences (Pages #7-8, Lines #103-109):

“These two procedures should be further studied to determine their specificity and sensitivity for diabetic retinopathy evaluations. The mechanisms that support the results of both tests should be different. For contrast sensitivity measurements, the visual response is mediated by mechanisms working within threshold levels, while for colour vision evaluation estimated using the Farnsworth–Munsell 100 hue test, there are many additional mechanisms working at suprathreshold levels. Therefore, both tests could show different or complementary neural impairment.”

4) The authors employ the Ishihara plates test to exclude congenital deficiency. How specific is the Ishihara plates test at differentiating between acquired and congenital loss of red – green colour vision?

A) We corrected the sentence. We inserted the following sentence (Page #9, Line #136):

“In addition, the Ishihara plates test was applied as a screening procedure to identify subjects with some degree of red-green colour vision loss.”

5) State type of LCD monitor / manufacturer / grey levels per gun / and calibration procedure.

A) We inserted in the Methods section the following sentences (Page #9, Line #146):

“All stimuli were displayed on a 21-inch colour LCD monitor (spatial resolution of 1280 × 1200 pixels, 75 Hz, 8 bits, Ecofit P2270 model; Samsung, Seoul, South Korea) in a dark room. A dithering routine was used to obtain additional grey levels [27]. Luminance linearization was performed by gamma correction using a colorimeter (CS100-A; Konica Minolta, Osaka, Japan).”

6) The 100 Hue test is also simulated on a visual display. One must be more specific as to what one means by 30% colour saturation. Is the display based 100 Hue simulation equivalent to the Munsell based 100 hue test illuminated with D65? If not, the differences should be discussed briefly in relation to acquired loss.

A) The computerized FM100 is equivalent to the original set illuminated by standard lighting. We rewrote this sentence in the Methods section as follows (Page #10, Line #162):

“For the FM 100 test, the subject was positioned at a 1 m distance from the monitor. The stimulus was composed of 85 circles of different hues, saturated colours, 1° of visual angle, and 42 cd/m2 of luminance. The computerized test was equivalent to the original test illuminated by D65, and was previously applied in other clinical investigations [27, 29].”
7) Also, some explanation as to how the log of the 100 hue score captures red-green and yellow-blue losses.
   
   A) We used the log-transformation only to permit the application of parametric statistical tests. We inserted the following sentence (Page #10, Line #170):
   “The log-transformation in both the results of contrast sensitivity test and the FM 100 hue test were used to meet the assumptions of parametric statistical tests [27].”

8) The loss of contrast sensitivity is surprisingly small when the diabetics and compared to normal subjects. The variability is also very large. This may be because of the large stimulus size employed in the test and differences in criteria when sinusoidal gratings are employed. To add value to the manuscript, it may be worth commenting on the advantages / disadvantages of using gratings and a number of different spatial frequencies (which for the patient is a long and demanding test) or letters / Landolt rings of fixed size and variable contrast (which is a more reliable and rapid test). Such a comparison is likely to be of interest to clinicians / ophthalmologists.
   
   A) We inserted the following sentences to address these concerns (Page #16, Line #300):
   “For the investigation of luminance contrast sensitivity, we used sinusoidal gratings at several spatial frequencies as stimuli to detect the contrast threshold. Other studies with diabetic patients applied different stimuli configurations to estimate contrast threshold [25, 37-40]. However, the use of sinusoidal grating was important because the visual system had different channels for spatial frequency processing. It is still not clear which channels would be impaired in diabetics. Different studies showed deficits in the contrast sensitivity estimated at different ranges of spatial frequency [14, 16, 41]. In diabetic patients, the reduction of the contrast sensitivity occurred even when the visual acuity was preserved [42, 43].”

9) One thing that emerges clearly from the study are the difficulties and variability of the 100-hue and CS test with sinusoidal gratings. Definitely worth more in depth discussion.
   
   A) To address this concern we inserted in the Discussion section a sentence about the difficulties in using both tests (Page #15, Line #276):
   “In this study we analysed two commonly used visual tests to evaluate the visual functions of diabetic patients. Both tests have advantages and disadvantages that apply to diabetic patients. An important disadvantage is that both tests required long testing time periods and were very demanding in terms of the patient’s attention and commitment. These factors may have contributed to the data variability. However, the visual tests have been applied in several studies, and our results could be directly compared with previously reported results. Few studies have incorporated both tests and correlated each result for the same patient groups. We suggest that our findings were important because they showed that patients without retinopathy may develop visual function impairment even before the clinical symptoms appear, and that contrast sensitivity and colour vision results can be used as clinical measurements to identify the status of the visual function of the newly diagnosed diabetic patient.”

10) It is also difficult to understand what is really useful in showing the differences in the ellipse plots in Fig. 3c. More discussion is needed to show the benefits.
A) To address this question we inserted in the Discussion section the following sentences (Page #18, Line #348):

“The ellipses represented the area where most of the results for each group of patients could be found. We observed an overlapping area in the results from two-dimensional space, which we considered as an intermediate risk area for a newly diagnosed patient. The areas without overlap between the groups could be considered to indicate high (exclusive diabetic area) or low (exclusive control area) risk to develop visual loss due to diabetes.”

11) In conclusion, the paper makes a useful contribution to our understanding of CS and CV changes in diabetes, but the discussion is not sufficiently critical of the techniques employed and the value of the results obtained. It would be useful to acknowledge and compare other tests of CS and CV (such as the Pelli-Robson test chart, CRS and the CAD test which is also used widely in clinical work) which may yield more useful results in diabetes and are also easier to use and the results easier to interpret.

A) To address the suggestions, we inserted in the Discussion section the following sentences (Page #17, Line #323):

“In another study using the colour vision assessment (CAD) test it was observed that diabetic subjects exhibited equal and highly correlated reduction in red-green and blue-yellow thresholds [24]. It may not be possible to directly compare the results from FM100 with other tests such as CCT and CAD. The task in FM100 is performed at suprathreshold levels, while for CAD and CCT the final results are estimated for the threshold level. CAD and CCT investigate the functioning of cells or neuronal processing with highest sensitivity, while in the FM100 test it is possible that more cells or neuronal processes than those with high sensitivity may contribute to the patient’s performance.”

12) Greater criticism is also needed when examining the correlation between CS and CV losses and changes in metabolic markers. If there is little or no correlation, one should say so and attempt to account for such findings.

A) We have addressed the reviewer’s suggestion and made changes in the Discussion section as follows (Page #18, Line #362):

“However, there was no complete correlation between metabolic markers and psychophysical performance. Previous studies reported both positive and negative correlations between the level of metabolic markers and psychophysical parameters [14, 17, 24, 44] while others found no correlation [53]. The variability of the clinical status from patients investigated across the different studies makes it more difficult to draw conclusions about the significance of these correlations. Higher values for time of diagnosis, glycated haemoglobin levels, or fasting blood glucose indicated poor control of glucose levels and this could be associated with a higher risk of vascular damage [54]. We found more significant correlations between contrast sensitivity and the metabolic markers from eyes without retinopathy. In addition, we found that the higher the value for metabolic markers, the worse the psychophysical performance. The impairment of glycaemic control alters neuronal function by both direct and indirect mechanisms. It is therefore possible that in eyes with retinopathy, the correlations between the visual performance and levels of metabolic markers could be nonlinear. Once the retinal damage occurs and the visual
function is lost, glycaemic control may have less influence on the residual visual functions.”

13) **Level of interest**: An article of importance in its field.
   A) Thank you.

14) **Quality of written English**: Needs some language corrections before being published.
   A) We have used a professional editing service.

15) **Statistical review**: No, the manuscript does not need to be seen by a statistician.
   A) Thank you.

16) **Declaration of competing interests**: None.
   A) This has been added.
Reviewer’s Report – Jonathan M. Gibson

Title: Influence of retinopathy on the achromatic and chromatic vision of patients with type 2 diabetes
Version: 2
Date: 17th June 2014

General Comments
1) The authors report a study of measuring colour vision with the FM 100 Test and Contrast Sensitivity in 27 Diabetic patients with and without retinopathy and 32 age matched controls. There is a considerable amount of existing work on colour vision in diabetes and I was not clear what this paper adds.
   A) To address this concern, we inserted a sentence in the Discussion section as follows (Page #18, Line #340):
   “Because the interpretation of the contrast sensitivity test and the FM100 hue test results in diabetic patients with and without retinopathy are still controversial, we correlated the results of both tests in the same group of diabetic patients and in controls, to evaluate how the results changed.”
   And (Page #18, Line #348):
   “The ellipses represented the area where most of the results for each group of patients could be found. We observed an overlapping area in the results from two-dimensional space, which we considered as an intermediate risk area for a newly diagnosed patient. The areas without overlap between the groups could be considered to indicate high (exclusive diabetic area) or low (exclusive control area) risk to develop visual loss due to diabetes.”

2) Many of the references are quite old.
   A) We have inserted updated references.

Major Compulsory Revisions
3) The paper is generally rather difficult to read and the discussion is poor, with the reader left unclear as to the significance of the findings and asking "so what."
   A) To address these concerns, we wrote new sentences in the Introduction and Discussion sections in order to clarify our purposes. These are discussed below.

4) The authors fail to develop an argument regarding the relevance of their findings. For example what is the importance of psychophysical testing in diabetic patients - is it to detect those patients who might develop retinopathy later, in a pre-clinical phase ? Or does it demonstrate that diabetic retinopathy has a neurological rather than microvascular basis?
   A) To answer the reviewer’s questions, we wrote a sentence in the Discussion section to clarify as follows (Page #15, Line #283):
   “We suggest that our findings were important because they showed that patients without retinopathy may develop visual function impairment even before the clinical symptoms appear, and that contrast sensitivity and colour vision results can be used as clinical
measurements to identify the status of the visual function of the newly diagnosed diabetic patient.”

5) The authors state "It has been reported that psychophysical measurements are of great value for monitoring the effects of diabetes on the visual system", but they fail to justify this statement.

A) To address this concern, we added to the Discussion a section to justify the importance of psychophysical measurements for diabetes monitoring. As an example, (Page #15, Line #273):

“Several studies identified visual losses of contrast sensitivity and colour vision associated with diabetes in the presence or absence of retinopathy, and used visual function as a biomarker to indicate the diabetic disease status [3,4,20-24].”

And (Page #15, Line #283):

“We suggest that our findings were important because they showed that patients without retinopathy may develop visual function impairment even before the clinical symptoms appear, and that contrast sensitivity and colour vision results can be used as clinical measurements to identify the status of the visual function of the newly diagnosed diabetic patient.”

Minor Essential Revisions

6) It was not clear to me in the exclusions section whether patients who had received laser were excluded from recruitment - this would be important as laser is known to affect colour vision. Also whether persons with cataracts were excluded.

A) We inserted in the Methods section the following sentences (Page #9, Line #139):

“Exclusion criteria included visual acuity of 20/40 or worse, congenital colour blindness, history of ophthalmological disease, advanced cataracts, and/or any chronic disease not associated with diabetes that could affect the visual system. None of the patients had previously received laser photocoagulation treatment.”

7) The article is written in US English and may need changing to UK English - i.e. color to colour, etc…

A) This was done.

8) Level of interest: An article of limited interest.

A) Thank you for your comment.

9) Quality of written English: Needs some language corrections before being published.

A) We have used a professional editing service for this revised manuscript.

10) Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

A) Thank you for your comment.

11) Declaration of competing interests: I declare that I have no competing interests.

A) This has been added.